

**SUBSTITUTED 3-CARBONYL-1H-INDOL-1-YL ACETIC ACID DERIVATIVES AS
INHIBITORS OF PLASMINOGEN ACTIVATOR INHIBITOR-1 (PAI-1)**

This application claims priority from co-pending provisional application serial number 60/432,107 filed on December 10, 2002, the entire disclosure of which is hereby incorporated by reference.

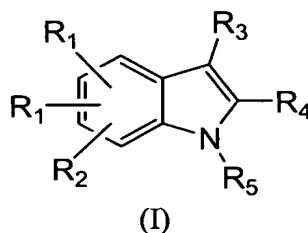
This invention relates to substituted 3-carbonyl-1H-indol-1-yl acetic acid derivatives as inhibitors of plasminogen activator inhibitor-1 (PAI-1) and as therapeutic compositions for treating conditions resulting from fibrinolytic disorders such as deep vein thrombosis and coronary heart disease, and pulmonary fibrosis.

BACKGROUND OF INVENTION

Plasminogen activator inhibitor-1 (PAI-1) is a major regulatory component of the plasminogen-plasmin system. PAI-1 is the principal physiologic inhibitor of both tissue type plasminogen activator (tPA) and urokinase type plasminogen activator (uPA). Elevated plasma levels of PAI-1 have been associated with thrombotic events as indicated by animal experiments (Krishnamurti, *Blood*, 69, 798 (1987); Reilly, *Arteriosclerosis and Thrombosis*, 11, 1276 (1991); Carmeliet, *Journal of Clinical Investigations*, 92, 2756 (1993)) and clinical studies (Rocha, *Fibrinolysis*, 8, 294, 1994; Aznar, *Haemostasis* 24, 243 (1994)). Antibody neutralization of PAI-1 activity resulted in promotion of endogenous thrombolysis and reperfusion (Biemond, *Circulation*, 91, 1175 (1995); Levi, *Circulation* 85, 305, (1992)). Elevated levels of PAI-1 have also been implicated in diseases of women such as polycystic ovary syndrome (Nordt, *Journal of Clinical Endocrinology and Metabolism*, 85, 4, 1563 (2000)) and bone loss induced by estrogen deficiency (Daci, *Journal of Bone and Mineral Research*, 15, 8, 1510 (2000)). Accordingly, agents that inhibit PAI-1 would be of utility in treating conditions originating from fibrinolytic disorder such as deep vein thrombosis, coronary heart disease, pulmonary fibrosis, polycystic ovary

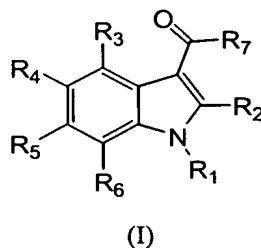
syndrome, etc.

WO 99/43654 and WO 99/43651 describe indole derivatives of formula I as inhibitors of phospholipase enzymes useful in preventing inflammatory conditions:



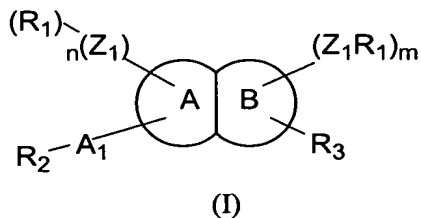
5

WO 2000/44743 discloses TGF- β production inhibitors of formula I:



where R_1 and R_2 are each independently hydrogen, optionally substituted alkyl, acyl, optionally substituted aryl or aromatic heterocyclic group and R_7 is an optionally substituted cyclic amino or azabicycloalkylamino.

WO 97/48697 describes substituted azabicyclic compounds inclusive of indoles, 2,3-dihydro-1H-indoles, and benzimidazoles of formula (I) for the treatment of conditions ameliorated by the administration of an inhibitor of tumor necrosis factor:



where A is a five-membered aza heterocycle;

B is a six membered aza heterocycle or an optionally substituted benzene ring;

20

Z₁ is a chemical bond, O, S, or NH;

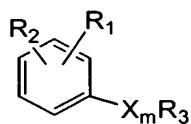
A₁ is a chemical bond, alkyl of 1-6 carbons, alkenylene of 2-6 carbons, or alkynylene of 2-6 carbons;

5 R₁ is hydrogen or optionally substituted alkyl of 2-6 carbons, lower alkenyl or lower alkynyl;

R₂ is hydrogen, alkenyl, alkyl, alkylsulfinyl, alkylsulphonyl, alkylthio, aryl, arylalkoxy, arylalkylsulphanyl, arylalkylsulphonyl, arylalkylthio, aryloxy, arylsulphanyl, arylsulphonyl, arylthio, -CN, cycloalkenyl, cycloalkenoxy, cycloalkyl, cycloalkyloxy, heteroaryl, heteroarylalkyloxy, heteroaryloxy, -OH, -SO₂NR₄R₅,
 10 -NR₄SO₂R₅, -NR₄R₅, -C(O)R₅, -C(O)C(O)R₅, -O(C=O) NR₄R₅, -C(O)OR₅, or -O(C=O)NR₄R₅, and

R₃ is carboxamide, acyl, substituted alkenyl, substituted alkyl, acylamino, oximino, alkynyl, ketomethyl, aminoalkyl, sulfonylmethyl, sulfinylmethyl, CF₂OR, alkylamino, alkoxy, alkylsulfanyl, sulfinyl, acyloxy, sulfonyl, OCF₂R, azo,
 15 aminosulfonyl, sulfonylamino, or aminooxalyl.

US 5,612,360 describes tetrazolylphenyl-substituted heterocycles of formula (I) as angiotensin II inhibitors.



(I)

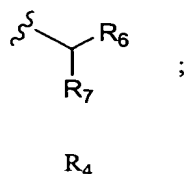
20 where: R₁ is -COOH, -S(O)₃H, -PO₃H₂, -C(O)NHSO₂R₈, or 5-tetrazolyl;

R₂ is hydrogen, -OH, -OAc, halogen, alkyl of 1-4 carbons, or alkoxy of 1-4 carbons;

R₃ is substituted benzimidazole, indazole, or



R₄ is:

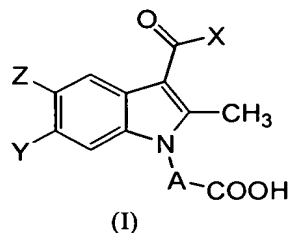


R₆ may be (CH₂)_pR₁, CONH(C₁ to C₄ alkyl), or CONH(C₁ to C₄ trifluoroalkyl) where p is 0, 1, 2, 3 or 4.

R₇ is alkyl, trifluoroalkyl, alkenyl, or trifluoroalkenyl all of 4-9 carbons;

R₁₁ is hydrogen, alkyl of 1-4 carbons, halogen, or (CH₂)_nphenyl; X is -(CH₂)_mCONH-, -(CH₂)_mNHCO-, -CH₂-, -O-, -NH-, or -(CH₂)_mCO-; and m is 0 or 1, where m is 0 or 1 and n is 1, 2 or 3.

FR 2,054,450 describes carboxymethyl indoles of formula (I) as anti-inflammatory agents:



where: A is linear alkyl;

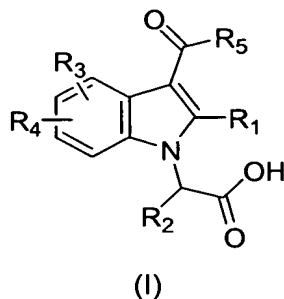
X is phenyl, optionally substituted with chlorine, alkyloxy, alkylthio, or alkylsulfonyl;

Y is alkyl; and

Z is hydrogen or alkyloxy.

SUMMARY OF THE INVENTION

This invention relates to compounds of formula (I):



wherein:

R_1 is hydrogen, C_2 - C_6 alkyl, C_3 - C_6 cycloalkyl, $-CH_2$ - C_3 - C_6 cycloalkyl, or C_1 - C_3 perfluoroalkyl, wherein the alkyl and cycloalkyl groups may be optionally substituted with halogen, $-CN$, C_1 - C_6 alkoxy, $-OH$, $-NH_2$, or $-NO_2$;

R_2 is hydrogen, C_1 - C_8 alkyl, C_3 - C_6 cycloalkyl, $-CH_2$ - C_3 - C_6 cycloalkyl, thienyl, CH_2 -thienyl, furanyl, CH_2 -furanyl, oxazolyl, CH_2 -oxazolyl, phenyl, benzyl, CH_2 -naphthyl, wherein the alkyl group and rings of the cycloalkyl, thienyl, furanyl, oxazolyl, phenyl, benzyl, and naphthyl groups may be optionally substituted with from 1 to 3 groups selected from halogen, C_1 - C_3 alkyl, C_1 - C_3 perfluoroalkyl, O - C_1 - C_3 perfluoroalkyl, S - C_1 - C_3 perfluoroalkyl, C_1 - C_3 alkoxy, $-OCHF_2$, $-CN$, $-COOH$, $-CH_2CO_2H$, $-C(O)CH_3$, $-CO_2R_6$, $-C(O)NH_2$, $-S(O)_2CH_3$, $-OH$, $-NH_2$, or $-NO_2$;

R_3 is hydrogen, halogen, C_1 - C_6 alkyl, C_1 - C_3 perfluoroalkyl, preferably $-CF_3$, C_1 - C_6 alkoxy, C_3 - C_6 cycloalkyl, $-CH_2$ - C_3 - C_6 cycloalkyl, $-NH_2$, or $-NO_2$;

R_4 is C_3 - C_8 alkyl, C_3 - C_6 alkenyl, C_3 - C_6 alkynyl, C_3 - C_6 cycloalkyl, $-CH_2$ - C_3 - C_6 cycloalkyl, thienyl, furanyl, oxazolyl, phenyl, benzo[*b*]furan-2-yl, benzo[*b*]thien-2-yl, benzo[1,3]dioxol-5-yl, naphthyl, wherein the alkyl group and the rings of the cycloalkyl, thienyl, furanyl, oxazolyl, phenyl, benzofuranyl, benzothienyl, and naphthyl groups may be optionally substituted by from 1 to 3 groups selected from halogen, C_1 - C_3 alkyl, C_1 - C_3 perfluoroalkyl, O - C_1 - C_3 perfluoroalkyl, S - C_1 - C_3 perfluoroalkyl, C_1 - C_3

alkoxy, -OCHF₂, -CN, -COOH, CH₂CO₂H, -C(O)CH₃, -C(O)OR₆, -C(O)NH₂, -S(O)-
 2CH₃, -OH, -NH₂, or -NO₂;

R₅ is C₁-C₈ alkyl, C₃-C₆ cycloalkyl, -CH₂-C₃-C₆ cycloalkyl, pyridinyl, -CH₂-
 5 pyridinyl, thienyl, CH₂-thienyl, furanyl, CH₂-furanyl, oxazolyl, CH₂-oxazolyl, phenyl,
 benzyl, benzo[*b*]furan-2-yl, benzo[*b*]thien-2-yl, benzo[1,3]dioxol-5-yl, naphthyl, CH₂-
 naphthyl, 9*H*-fluoren-1-yl, 9*H*-fluoren-4-yl, 9*H*-fluoren-9-yl, 9-fluorenone-1-yl, 9-
 fluorenone-2-yl, 9-fluorenone-4-yl, CH₂-9*H*-fluoren-9-yl, wherein the alkyl group and
 the rings of the cycloalkyl, pyridinyl, thienyl, furanyl, oxazolyl, phenyl, benzyl,
 10 benzofuranyl, benzothienyl, naphthyl, fluorenyl, and fluorenone groups may be
 optionally substituted by from 1 to 3 groups selected from halogen, C₁-C₃ alkyl, C₃-C₆
 cycloalkyl, C₁-C₃ perfluoroalkyl, -O-C₁-C₃ perfluoroalkyl, -S-C₁-C₃ perfluoroalkyl,
 C₁-C₃ alkoxy, phenoxy, -OCHF₂, -CN, -COOH, -CH₂CO₂H, -C(O)CH₃, -CO₂R₆,
 -C(O)NH₂, -S(O)₂CH₃, -OH, -NH₂, or -NO₂, wherein the phenoxy group may be
 15 optionally substituted by from 1 to 3 groups selected from halogen, C₁-C₃ alkyl, or
 C₁-C₃ perfluoroalkyl; and

R₆ is C₁-C₆ alkyl, C₃-C₆ cycloalkyl, -CH₂-C₃-C₆ cycloalkyl, or benzyl;

20 or a pharmaceutically acceptable salt or ester form thereof.

DETAILED DESCRIPTION OF THE INVENTION

Preferred compounds of the present invention are those of formula (I)
 25 wherein R₁-R₃ and R₅-R₆ are as defined above, and

R₄ is thienyl, furanyl, oxazolyl, phenyl, benzo[*b*]furan-2-yl,
 benzo[*b*]thien-2-yl, benzo[1,3]dioxol-5-yl or naphthyl, wherein the rings of the thienyl,
 furanyl, oxazolyl, phenyl, benzofuranyl, benzothienyl, and naphthyl groups may be
 30 optionally substituted by from 1 to 3 groups selected from halogen, C₁-C₃ alkyl, C₁-C₃
 perfluoroalkyl, -O-C₁-C₃ perfluoroalkyl, -S-C₁-C₃ perfluoroalkyl, C₁-C₃ alkoxy, -OCHF₂,
 -CN, -COOH, -CH₂CO₂H, -C(O)CH₃, -CO₂R₆, -C(O)NH₂, -S(O)₂CH₃, -OH, -NH₂, or
 -NO₂;

or a pharmaceutically acceptable salt or ester form thereof.

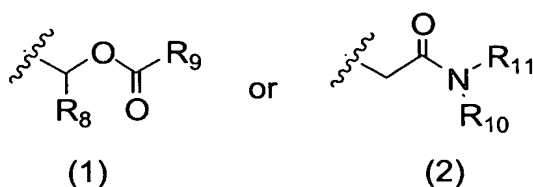
Specific compounds according to this invention include:

- 5 [3-(4-chlorobenzoyl)-5-(4-chlorophenyl)-1H-indol-1-yl] acetic acid;
 [3-(benzo[b]thiophene-2-carbonyl)-5-(4-methylphenyl)-1H-indol-1-yl] acetic
 acid; and
 [3-(4-chlorobenzoyl)-5-(4-methylphenyl)-1H-indol-1-yl] acetic acid, or a
 pharmaceutically acceptable salt or ester form thereof.

10

 The preferred salt forms of the compounds herein include but are not limited to sodium salts, and potassium salts. Other useful salt forms of these compounds include those formed with pharmaceutically acceptable inorganic and organic bases known in the art. Salt forms prepared using inorganic bases include hydroxides,
 15 carbonates or bicarbonates of the therapeutically acceptable alkali metals or alkaline earth metals, such as sodium potassium, magnesium, calcium and the like. Acceptable organic bases include amines, such as benzylzmine, mono-, di- and trialkylamines, preferably those having alkyl groups of from 1 to 6 carbon atoms, more preferably 1 to 3 carbon atoms, such as methylamine, dimethylamine,
 20 trimethylamine, ethylamine, diethylamine, triethylamine, mono-, di-, and triethanolamine. Also useful are alkylene diamines containing up to 6 carbon atoms, such as hexamethylenediamine; cyclic saturated or unsaturated bases containing up to 6 carbon atoms, including pyrrolidine, piperidine, morpholine, piperazine and their N-alkyl and N-hydroxyalkyl derivatives, such as N-methyl-morpholine and N-(2-
 25 hydroxyethyl)-piperidine, or pyridine. Quaternary salts may also be formed, such as tetralkyl forms, such as tetramethyl forms, alkyl-alkanol forms, such as methyl-triethanol or trimethyl-monoethanol forms, and cyclic ammonium salt forms, such as N-methylpyridinium, N-methyl-N-(2-hydroxyethyl)-morpholinium, N,N-di-methylmorpholinium, N-methyl-N-(2-hydroxyethyl)-morpholinium, or N,N-dimethyl-
 30 piperidinium salt forms. These salt forms may be prepared using the acidic compound(s) of Formula I and procedures known in the art.

- Ester forms of the compounds of this invention include straight chain alkyl esters having from 1 to 6 carbon atoms or branched chain alkyl groups containing 3 or 6 carbon atoms, including methyl, ethyl, propyl, butyl, 2-methylpropyl and 1,1-dimethylethyl esters. Other esters useful with this invention include those of the
- 5 formula $-\text{COOR}_7$ wherein R_7 is selected from the formulae:



- 10 wherein R_8 , R_9 , R_{10} , R_{11} are independently selected from hydrogen, alkyl of from 1 to 10 carbon atoms, aryl of 6 to 12 carbon atoms, arylalkyl of from 6 to 12 carbon atoms; heteroaryl or alkylheteroaryl wherein the heteroaryl ring is bound by an alkyl chain of from 1 to 6 carbon atoms.

- 15 Among the preferred ester forms of the compounds herein include but not limited to C_1 - C_6 alkyl esters, C_3 - C_6 branched alkyl esters, benzyl esters, etc.

- As used herein, the terms alkyl, alkenyl and alkynyl include both straight chain as well as branched claim chains. Preferably, the C_1 - C_3 perfluoroalkyl
- 20 substituent is $-\text{CF}_3$; the $-\text{O}-\text{C}_1$ - C_3 perfluoroalkyl substituent is OCF_3 ; and the $-\text{S}-\text{C}-\text{C}_3$ perfluoroalkyl substituent is $-\text{SCF}_3$.

- As used herein, "aryl" refers to an unsaturated aromatic carbocyclic group of from 6 to 14 carbon atoms having a single ring (e.g., phenyl) or multiple condensed
- 25 (fused) rings (e.g., naphthyl or anthryl). Preferred aryl groups include phenyl, naphthyl and the like. As used herein, "heteroaryl" refers to a monocyclic or bicyclic aromatic group of from 1 to carbon atoms and 1 to 4 heteroatoms selected from oxygen, nitrogen and sulfur within at least one ring (if there is more than one ring). Such heteroaryl groups can have a single ring, such as pyridyl, pyrrolyl or furyl

groups, or multiple condensed rings, such as indolyl, indoliziny, benzofuranyl or benzothienyl groups. Preferred heteroaryls include pyridyl, pyrrolyl and furyl.

Unless otherwise limited by the definition for the aryl or heteroaryl groups herein, such groups can optionally be substituted with from 1 to 5 substituents selected from the group consisting of acyloxy, hydroxy, acyl, alkyl of 1 to 6 carbon atoms, alkoxy of 1 to 6 carbon atoms, alkenyl of 2 to 6 carbon atoms, alkynyl of 2 to 6 carbon atoms, substituted alkyl, substituted alkoxy, substituted alkenyl, substituted alkynyl, amino, amino substituted by one or two alkyl groups of from 1 to 6 carbon atoms, aminoacyl, acylamino, azido, cyano, halo, nitro, thioalkoxy of from 1 to 6 carbon atoms, substituted thioalkoxy of from 1 to 6 carbon atoms, and trihalomethyl. Substituents on the alkyl, alkenyl, alkynyl, thioalkoxy and alkoxy groups mentioned above include halogens, CN, OH, and amino groups. Preferred substituents on the aryl groups herein include alkyl, alkoxy, halo, cyano, nitro, trihalomethyl, and thioalkoxy.

The compounds of the present invention are inhibitors of the serine protease inhibitor PAI-1, and are therefore useful in the treatment, inhibition, prevention or prophylaxis in a mammal, preferably in a human, of those processes which involve the production and/or action of PAI-1. Thus, the compounds of the invention are useful in the treatment or prevention of noninsulin dependent diabetes mellitus and cardiovascular disease caused by such condition, and prevention of thrombotic events associated with coronary artery and cerebrovascular disease. These compounds are also useful for inhibiting the disease process involving the thrombotic and prothrombotic states which include, but are not limited to, formation of atherosclerotic plaques, venous and arterial thrombosis, myocardial ischemia, atrial fibrillation, deep vein thrombosis, coagulation syndromes, pulmonary fibrosis, cerebral thrombosis, thromboembolic complications of surgery (such as joint replacement), and peripheral arterial occlusion. These compounds are also useful in treating stroke associated with or resulting from atrial fibrillation.

The compounds of the invention may also be used in the treatment of diseases associated with extracellular matrix accumulation, including, but not limited

to, renal fibrosis, chronic obstructive pulmonary disease, polycystic ovary syndrome, restenosis, renovascular disease and organ transplant rejection.

5 The compounds of the invention may also be used in the treatment of malignancies, and diseases associated with neoangiogenesis (such as diabetic retinopathy).

10 The compounds in the invention may also be used in conjunction with and following processes or procedures involving maintaining blood vessel patency, including vascular surgery, vascular graft and stent patency, organ, tissue and cell implantation and transplantation.

15 The compounds in the invention may also be useful in the treatment of inflammatory diseases, septic shock and the vascular damage associated with infections.

20 The compounds of the invention are useful for the treatment of blood and blood products used in dialysis, blood storage in the fluid phase, especially ex vivo platelet aggregation. The present compounds may also be added to human plasma during the analysis of blood chemistry in hospital settings to determine the fibrinolytic capacity thereof.

25 The compounds in the present invention may also be used in combination with prothrombolytic, fibrinolytic and anticoagulant agents.

 The compounds of the present invention may also be used to treat cancer including, but not limited to, breast and ovarian cancer, and as imaging agents for the identification of metastatic cancers.

30 The compounds of the invention may also be used in the treatment of Alzheimer's disease. This method may also be characterized as the inhibition of plasminogen activator by PAI-1 in a mammal, particularly a human, experiencing or subject to Alzheimer's disease. This method may also be characterized as a method

of increasing or normalizing levels of plasmin concentration in a mammal, particularly those experiencing or subject to Alzheimer's disease.

5 The compounds of the invention may be used for the treatment of myelofibrosis with myeloid metaplasia by regulating stromal cell hyperplasia and increases in extracellular matrix proteins.

10 The compounds of the invention may also be used in conjunction with protease inhibitor - containing highly active antiretroviral therapy (HAART) for the treatment of diseases which originate from fibrinolytic impairment and hyper-coagulability of HIV-1 infected patients receiving such therapy.

15 The compounds of the invention may be used for the treatment of diabetic nephropathy and renal dialysis associated with nephropathy.

20 The compounds of the invention may be used to treat cancer, septicemia, obesity, insulin resistance, proliferative diseases such as psoriasis, improving coagulation homeostasis, cerebrovascular diseases, microvascular disease, hypertension, dementia, osteoporosis, arthritis, asthma, heart failure, arrhythmia, angina, and as a hormone replacement agent, treating, preventing or reversing progression of atherosclerosis, Alzheimer's disease, osteoporosis, osteopenia; reducing inflammatory markers, reducing C-reactive protein, or preventing or treating low grade vascular inflammation, stroke, dementia, coronary heart disease, primary and secondary prevention of myocardial infarction, stable and unstable angina, 25 primary prevention of coronary events, secondary prevention of cardiovascular events, peripheral vascular disease, peripheral arterial disease, acute vascular syndromes, reducing the risk of undergoing a myocardial revascularization procedure, microvascular diseases such as nephropathy, neuropathy, retinopathy and nephrotic syndrome, hypertension, Type I and 2 diabetes and related diseases, 30 hyperglycemia, hyperinsulinemia, malignant lesions, premalignant lesions, gastrointestinal malignancies, liposarcomas and epithelial tumors, proliferative diseases such as psoriasis, improving coagulation homeostasis, and/or improving endothelial function, and all forms of cerebrovascular diseases.

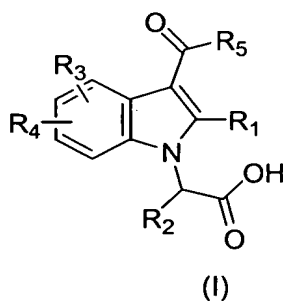
The compounds of the invention may be used for the topical applications in wound healing for prevention of scarring.

5 Methods for the treatment, inhibition, prevention or prophylaxis in a mammal of each of the conditions or maladies listed herein are part of the present invention. Each method comprises administering to a mammal in need thereof a pharmaceutically or therapeutically effective amount of a compound of this invention, or a pharmaceutically acceptable salt or ester form thereof.

10

Each of the methods described herein comprise administering to a mammal in need of such treatment a pharmaceutically effective amount of a compound of this invention, or a pharmaceutically acceptable salt or ester form thereof. It will be understood that a pharmaceutically effective amount of the compound will be at least
15 the minimum amount necessary to provide an improvement in the symptoms or underlying causation of the malady in question or to inhibit or lessen the onset of symptoms of the malady.

Accordingly the present invention further comprises a method of inhibiting in a
20 mammal plasminogen activator inhibitor type 1 (PAI-1) which comprises administering to a mammal in need thereof a pharmaceutically effective amount of a compound of Formula (I):



25

wherein,

R_1 is hydrogen, C_2 - C_6 alkyl, C_3 - C_6 cycloalkyl, $-CH_2$ - C_3 - C_6 cycloalkyl, or C_1 - C_3 perfluoroalkyl, wherein the alkyl and cycloalkyl groups may be optionally substituted with halogen, $-CN$, C_1 - C_6 alkoxy, $-OH$, $-NH_2$, or $-NO_2$;

R₂ is hydrogen, C₁-C₈ alkyl, C₃-C₆ cycloalkyl, -CH₂-C₃-C₆ cycloalkyl, thienyl, CH₂-thienyl, furanyl, CH₂-furanyl, oxazolyl, CH₂-oxazolyl, phenyl, benzyl, CH₂-naphthyl, wherein the alkyl group and rings of the cycloalkyl, thienyl, furanyl, oxazolyl, phenyl, benzyl, and naphthyl groups may be optionally substituted with from 1 to 3 groups selected from halogen, C₁-C₃ alkyl, C₁-C₃ perfluoroalkyl, O-C₁-C₃ perfluoroalkyl, S-C₁-C₃ perfluoroalkyl, C₁-C₃ alkoxy, -OCHF₂, -CN, -COOH, -CH₂CO₂H, -C(O)CH₃, -CO₂R₆, -C(O)NH₂, -S(O)₂CH₃, -OH, -NH₂, or -NO₂;

R₃ is hydrogen, halogen, C₁-C₆ alkyl, C₁-C₃ perfluoroalkyl, preferably -CF₃, C₁-C₆ alkoxy, C₃-C₆ cycloalkyl, -CH₂-C₃-C₆ cycloalkyl, -NH₂, or -NO₂;

R₄ is C₃-C₈ alkyl, C₃-C₆ alkenyl, C₃-C₆ alkynyl, C₃-C₆ cycloalkyl, -CH₂-C₃-C₆ cycloalkyl, thienyl, furanyl, oxazolyl, phenyl, benzo[b]furan-2-yl, benzo[b]thien-2-yl, benzo[1,3]dioxol-5-yl, naphthyl, wherein the alkyl group and the rings of the cycloalkyl, thienyl, furanyl, oxazolyl, phenyl, benzofuranyl, benzothienyl, and naphthyl groups may be optionally substituted by from 1 to 3 groups selected from halogen, C₁-C₃ alkyl, C₁-C₃ perfluoroalkyl, O-C₁-C₃ perfluoroalkyl, S-C₁-C₃ perfluoroalkyl, C₁-C₃ alkoxy, -OCHF₂, -CN, COOH, -CH₂CO₂H, -C(O)CH₃, -C(O)OR₆, -C(O)NH₂, -S(O)₂CH₃, -OH, -NH₂, or -NO₂;

R₅ is C₁-C₈ alkyl, C₃-C₆ cycloalkyl, -CH₂-C₃-C₆ cycloalkyl, pyridinyl, -CH₂-pyridinyl, thienyl, CH₂-thienyl, furanyl, CH₂-furanyl, oxazolyl, CH₂-oxazolyl, phenyl, benzyl, benzo[b]furan-2-yl, benzo[b]thien-2-yl, benzo[1,3]dioxol-5-yl, naphthyl, CH₂-naphthyl, 9H-fluoren-1-yl, 9H-fluoren-4-yl, 9H-fluoren-9-yl, 9-fluorenone-1-yl, 9-fluorenone-2-yl, 9-fluorenone-4-yl, CH₂-9H-fluoren-9-yl, wherein the alkyl group and the rings of the cycloalkyl, pyridinyl, thienyl, furanyl, oxazolyl, phenyl, benzyl, benzofuranyl, benzothienyl, naphthyl, fluorenyl, and fluorenone groups may be optionally substituted by from 1 to 3 groups selected from halogen, C₁-C₃ alkyl, C₃-C₆ cycloalkyl, C₁-C₃ perfluoroalkyl, -O-C₁-C₃ perfluoroalkyl, -S-C₁-C₃ perfluoroalkyl, C₁-C₃ alkoxy, phenoxy, -OCHF₂, -CN, -COOH, -CH₂CO₂H, -C(O)CH₃, -CO₂R₆, -C(O)NH₂, -S(O)₂CH₃, -OH, -NH₂, or -NO₂, wherein the phenoxy group may be optionally substituted by from 1 to 3 groups selected from halogen, C₁-C₃ alkyl, or C₁-C₃ perfluoroalkyl; and

R₆ is C₁-C₆ alkyl, C₃-C₆ cycloalkyl, -CH₂-C₃-C₆ cycloalkyl, or benzyl;

or a pharmaceutically acceptable salt or ester form thereof.

5

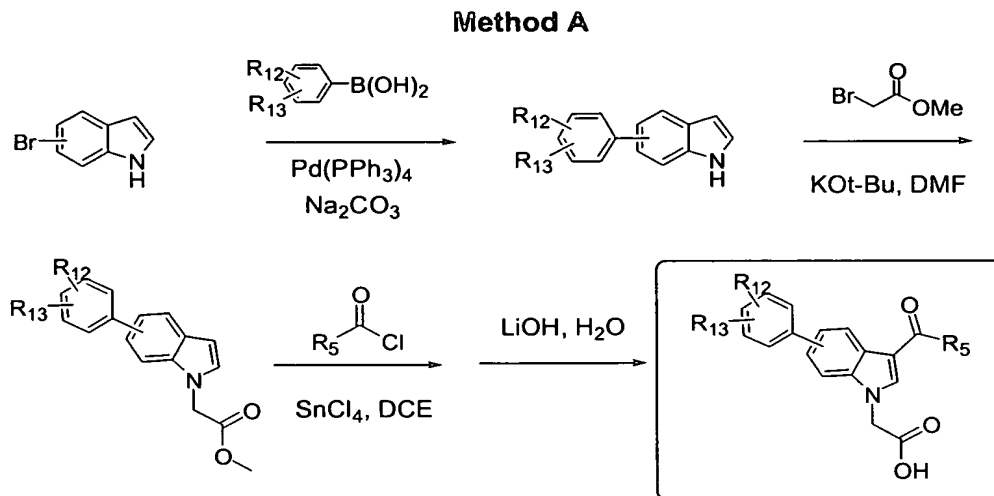
PROCESS OF THE INVENTION

The compounds of the present invention can be readily prepared according to the following reaction scheme or modification thereof as would be recognized by one skilled in the art using readily available starting materials, reagents and conventional synthetic procedures. It is also possible to make use of variants of these process steps, which in themselves are known to and well within the preparatory skill of the medicinal chemist. In the following reaction schemes, R₁-R₆ are selected from the groups defined above. R₁₂ and R₁₃ are each independently hydrogen, halogen, C₁-C₃ alkyl, C₁-C₃ perfluoroalkyl, preferably -CF₃, -O-C₁-C₃ perfluoroalkyl, preferably -OCF₃, -S-C₁-C₃ perfluoroalkyl, preferably -SCF₃, C₁-C₃ alkoxy, -OCHF₂, -C(O)CH₃, -C(O)NH₂, -S(O)₂CH₃, -OH, -NH₂, or -NO₂;

20 **Method A**

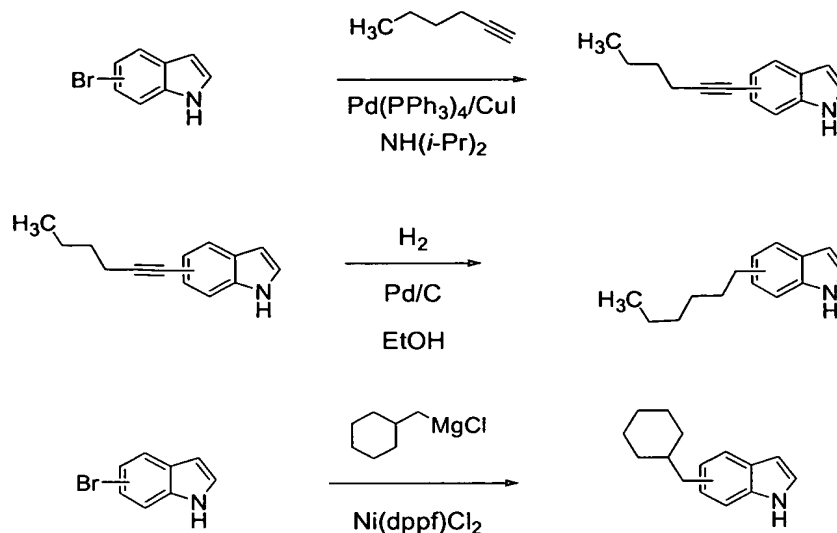
In Method A, indole, substituted on the benzene ring with bromide, iodine, or triflate, is cross-coupled with an aryl boronic acid in the presence of a palladium catalyst, such as Pd(PPh₃)₄, a base, such as Na₂CO₃ or NaHCO₃, in a solvent, such as water, dioxane, THF, toluene, methanol or ethanol, or in a mixed co-solvent system comprising two or more of the aforesaid solvents, at 50-110 °C. Boronic acid derivatives of benzene, furan, thiophene, benz[*b*]thiophene and naphthylene are described in the literature and many are presently commercially available. The resulting aryl substituted indole may be alkylated on nitrogen using methyl bromoacetate in the presence of a base, such as NaH or KO^{*t*}-Bu, in an inert solvent, such as THF or DMF. The resulting aryl indo-1-yl acetic acid methyl ester is acylated at the C-3 position by an acid chloride in a solvent, such as dichloromethane (DCM) or dichloroethane (DCE), in the presence of a Lewis acid, such as SnCl₄ at -40 to

+25 °C. The methyl ester may be hydrolyzed with base and purified by chromatography or by HPLC to afford the 1*H*-indol-1-yl acetic acid compounds.



Method B

Indoles containing alkyl, alkenyl and alkynyl substituents may also be prepared from indole substituted on the benzene ring with bromide, iodine, or triflate via palladium catalyzed coupling reaction with primary acetylenes. This reaction can be performed using a palladium catalyst, such as Pd(PPh₃)₄, a base, such as HN(*i*-Pr)₂ or EtN(*i*-Pr)₂, with or without a copper salt, such as CuI or CuBr, in an inert solvent, such as MeCN or toluene. The resulting alkynylindoles may be reduced to alkenyl- or alkylindoles by catalytic hydrogenation. Indoles substituted with alkyl, cycloalkyl, and benzyl groups can be prepared from the same substituted indoles by a nickel catalyzed coupling reaction. This reaction uses an alkylmagnesium coupling partner, such as C₆H₁₁CH₂MgCl, PhCH₂MgCl, or PhCMe₂CH₂MgCl and a nickel catalyst, such as Ni(dppf)Cl₂ (dppf = 1,1'-bis(diphenylphosphino)ferrocene) to give the corresponding substituted indoles. These indoles can then be further elaborated as described in Method A to give the desired indol-1-yl acetic acids.

Method B

5

This invention also provides pharmaceutical compositions comprising substituted 1*H*-indol-1-yl acetic acid derivatives of Formula I as described herein either alone or in combination with excipients (i.e. pharmaceutically acceptable materials with no pharmacological effects and pharmaceutically acceptable carriers).

10 A pharmaceutically or therapeutically effective amount of a compound of this invention refers to an amount of the compound which will sufficiently inhibit the severe protease inhibitor PAI - I in a mammal in need thereof to provide sufficient inhibition of PAI - I.

15 The precise dosage to be employed depends upon several factors including the host, whether in veterinary medicine or human medicine, the nature and severity of the condition being treated, the mode of administration and the particular active substance employed. The compounds may be administered by any conventional route, in particular enterally, preferably orally in the form of tablets or capsules.

20 Administered compounds can be in the free form or pharmaceutically acceptable salt form as appropriate, for use as a pharmaceutical, particularly for use in the prophylactic or curative treatment of atherosclerosis and sequelae (angina pectoris,

myocardial infarction, arrhythmias, heart failure, kidney failure, stroke, peripheral arterial occlusion, and related disease states). These measures will slow the rate of progress of the disease state and assist the body in reversing the process direction in a natural manner.

5

Any suitable carrier known to the art can be used to prepare the pharmaceutical compositions. In such a composition, the carrier may be a solid, liquid or mixture of a solid and a liquid. Solid compositions include powders, tablets and capsules. A solid carrier can be one or more substances which may also act as
10 a flavoring agent, lubricant, solubilizer, suspending agent, binder, or tablet disintegrant. In powders, the carrier is a finely divided solid, which is in admixture with the finely divided active ingredient. In tablets, the active ingredient is mixed with a carrier having the necessary binding properties in suitable proportions and compacted in the shape and size desired. Suitable solid carriers are magnesium
15 carbonate, magnesium stearate, talc, sugar, lactose, pectin, dextrin, starch, gelatin, tragacanth, methyl cellulose, hydroxymethyl cellulose, sodium carboxymethyl cellulose, a low melting wax, cocoa butter, and the like. Encapsulating materials may also be employed with the compounds of this invention, and the term "composition" is intended to include the active ingredient in combination with an encapsulating
20 material as a formulation, with or without other carriers. Cachets may also be used in the delivery of the anti-atherosclerotic medicament of this invention.

Sterile liquid compositions include solutions, suspensions, emulsions, syrups and elixirs. The compounds of this invention may be dissolved or suspended in the
25 pharmaceutically acceptable carrier, such as sterile water, sterile organic solvent or a mixture of both. Preferably the liquid carrier is one suitable for parental injection. Where the compounds are sufficiently soluble they can be dissolved directly in normal saline with or without the use of suitable organic solvents, such as propylene glycol or polyethylene glycol. If desired, dispersions of the finely divided compounds
30 can be made-up in aqueous starch or sodium carboxymethyl cellulose solution, or in a suitable oil, such as arachis oil. Liquid pharmaceutical compositions, which are sterile solutions or suspensions, can be utilized by intramuscular, intraperitoneal or

subcutaneous injection. In many instances a liquid composition form may be used instead of the preferred solid oral method of administration.

5 It is preferred to prepare unit dosage forms of the compounds for standard administration regimens. In this way, the composition can be subdivided readily into smaller doses at the physicians direction. For example, unit dosages may be made up in packeted powders, vials or ampoules and preferably in capsule or tablet form. The active compound present in these unit dosage forms of the composition may be present in an amount of from about one gram to about fifteen grams or more, for 10 single or multiple daily administration, according to the particular need of the patient. The daily dose of active compound will vary depending upon the route of administration, the size, age and sex of the patient, the severity of the disease state, and the response to the therapy as traced by blood analysis and the patients recovery rate. By initiating the treatment regimen with a minimal daily dose of about 15 one gram, the blood levels of PAI-1 and the patients symptomatic relief analysis may be used to determine whether a larger dose is indicated. Based upon the data presented below, the projected daily dose for both human and veterinary use will be from about 25 to about 200 milligrams/kilogram per day, and more usually, from about 50 to about 100 milligrams/kilogram per day.

20

The ability of the compounds of this invention to inhibit plasminogen activator inhibitor-1 was established by the following experimental procedures:

PRIMARY SCREEN FOR THE PAI-1 INHIBITION

25

Test compounds were dissolved in DMSO at a final concentration of 10mM, then diluted 100X in physiologic buffer. The inhibitory assay was initiated by the addition of the test compound (1 – 100 μ M final concentration, maximum DMSO concentration of 0.2%) in a pH 6.6 buffer containing 140 nM recombinant human plasminogen activator inhibitor-1 (*Molecular Innovations, Royal Oak, MI*). Following 30 a 1 hour incubation at room temperature, 70 nM of recombinant human tissue plasminogen activator (tPA) was added, and the combination of the test compound, PAI-1 and tPA was incubated for an additional 30 minutes. Following the second

incubation, Spectrozyme-tPA (*American Diagnostica, Greenwich, CT*), a chromogenic substrate for tPA, was added and absorbance was read at 405 nm at 0 and 60 minutes. Relative PAI-1 inhibition was equal to the residual tPA activity in the presence of the test compound and PAI-1. Control treatments included the complete inhibition of tPA by PAI-1 at the molar ratio employed (2:1), and the absence of any effect of the test compound on tPA alone.

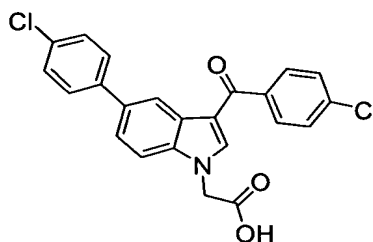
ASSAY FOR DETERMINING IC₅₀ OF INHIBITION OF PAI-1

This assay was based upon the non-SDS dissociable interaction between tPA and active PAI-1. Assay plates were initially coated with human tPA (10 µg/ml). The test compounds were dissolved in DMSO at 10 mM, then diluted with physiologic buffer (pH 7.5) to a final concentration of 1-50µM. The test compounds were incubated with human PAI-1 (50 ng/ml) for 15 minutes at room temperature. The tPA-coated plate was washed with a solution of 0.05% Tween 20 and 0.1% BSA, then the plate was blocked with a solution of 3% BSA. An aliquot of the test compound/PAI-1 solution was then added to the tPA-coated plate, incubated at room temperature for 1 hour and washed. Active PAI-1 bound to the plate was assessed by adding an aliquot of a 1:1000 dilution of the 33B8 monoclonal antibody against human PAI-1, and the plate was incubated at room temperature for 1 hour (*Molecular Innovations, Royal Oak, MI*). The plate was again washed, and a solution of goat anti-mouse IgG-alkaline phosphatase conjugate was added at a 1:50,000 dilution in goat serum. The plate was incubated 30 minutes at room temperature, washed, and a solution of alkaline phosphatase substrate was added. The plate was incubated 45 minutes at room temperature, and color development was determined at OD_{405nm}. The quantitation of active PAI-1 bound to tPA at varying concentrations of test compound was used to determine the IC₅₀. Results were analyzed using a logarithmic best-fit equation. The assay sensitivity was 5 ng/ml of human PAI-1 as determined from a standard curve ranging from 0-100 ng/ml.

The compounds of the present invention inhibited Plasminogen Activator Inhibitor-1 as summarized in Table I.

Table 1. Inhibition of Plasminogen Activator Inhibitor-1 by Examples 1-3

<i>Example</i>	<i>% Inhibition @ 25 μM</i>
1	47
2	45
3	46

5 **Example 1:****[3-(4-chlorobenzoyl)-5-(4-chlorophenyl)-1H-indol-1-yl]acetic acid**

Step 1:

A stirred slurry of 6.35 g (60 mmol) K_2CO_3 , 2.94 g (15 mmol) 5-bromoindole,
 10 2.50 g (16 mmol) 4-chlorophenylboronic acid, and 0.48 g (0.42 mmol)
 tetrakis(triphenylphosphine) palladium was heated to reflux for 2 ½ hours. The reaction
 mixture was allowed to cool and was then poured into 200 ml water and extracted
 with EtOAc. The organic layer was separated, dried over $MgSO_4$, and concentrated.
 The residue was chromatographed on silica to afford 1.39 g 5-(4-chlorophenyl)indole
 15 as a white solid.

Step 2:

To a solution of 0.68 g (3.0 mmol) 5-(4-chlorophenyl)indole in 20 ml
 anhydrous DMF was added 3.1 ml 1.0 M solution of $KOt-Bu$ in THF. The solution was
 20 stirred at room temperature for 15 min and then 0.29 ml (3.1 mmol) methyl
 bromoacetate was added. The solution was stirred at room temperature overnight.
 The solution was concentrated under vacuum and the residue was dissolved in a
 minimal amount of EtOAc. This solution was washed once with water and the organic
 phase was decanted from the aqueous phase with a pipet and loaded directly on a
 25 column of silica where it was chromatographed using 15-25% EtOAc-hexane. This
 afforded 0.485 g [5-(4-chloro-phenyl)-indol-1-yl]-acetic acid methyl ester as a solid.

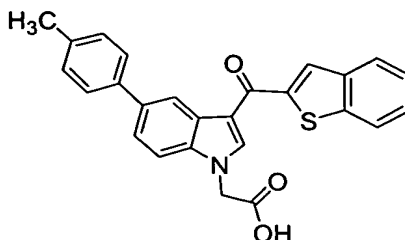
Step 3:

To a solution of 0.485 g (1.61 mmol) product from Step 2 and 0.24 ml (1.9 mmol) 4-chlorobenzoyl chloride in 10 ml dichloroethane, cooled to 0 °C in ice, was added 1.9 ml 1.0 M solution SnCl₄ in DCM. The ice bath was removed and the reaction allowed to stir at room temperature overnight. The solution was poured into saturated aqueous NaHCO₃ with stirring and the solution was extracted with EtOAc. The organic phase was dried over MgSO₄ and concentrated. The residue was chromatographed on silica using 20-40% EtOAc-hexane to afford a solid which was triturated from diethyl ether to afford 0.30 g [3-(4-chloro-benzoyl)-5-(4-chloro-phenyl)-indol-1-yl]-acetic acid methyl ester as colorless crystals.

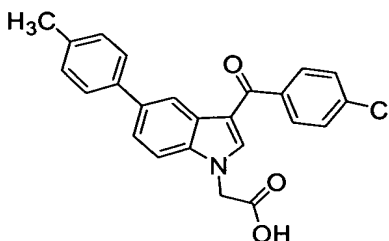
Step 4:

To a solution of 0.30 g (0.68 mmol) product from Step 3 in 5 ml THF was added a solution of 0.11 g (2.72 mmol) lithium hydroxide hydrate in 5 ml water. The solution was stirred at room temperature overnight, acidified with 4 ml 1 N aqueous HCL, diluted with water, and extracted once each with dichloromethane and EtOAc. The combined organic extracts were concentrated and the residue was purified by RP-HPLC to afford 0.106 g **Example 1**: mp 255-257 °C; ¹H NMR (DMSO-*d*₆, 300 MHz) δ 5.20 (s, 2H), 7.54 (d, *J*= 8.4 Hz, 2H), 7.58-7.71 (m, 4H), 7.72 (d, *J*= 8.7 Hz, 2H) 7.82 (d, *J*= 8.4 Hz, 2H), 8.16 (s, 1H), 8.52 (s, 1H); MS: *m/z* (ESI) 422 (M-H); Anal. calcd for (C₂₃H₁₅Cl₂NO₃) C, H, N.

The compounds of Examples 2 and 3 were prepared by the method used to prepare the compound of Example 1, using 5-bromoindole, 4-methylbenzeneboronic acid, benzo[b]thiophene-2-carbonyl chloride, and 4-chlorobenzoyl chloride and purified by semi-preparative RP-HPLC¹.

Example 2:**[3-(Benzo[*b*]thiophene-2-carbonyl)-5-(4-methylphenyl)-1*H*-indol-1-yl]-acetic acid**

5

MS: *m/z* (ESI) 426 (M+H); LCMS² retention time: 2.15 min.**Example 3:****[3-(4-chlorobenzoyl)-5-(4-methylphenyl)-1*H*-indol-1-yl]-acetic acid**

15

MS: *m/z* (ESI) 426 (M+H); LCMS² retention time: 1.85 min.**Notes:****1. Semi-preparative RP-HPLC conditions:**

Gilson Semi-Preparative HPLC system with Unipoint Software

20 Column: Phenomenex C18 Luna 21.6 mm x 60 mm, 5 μ M; Solvent A: Water (0.02% TFA buffer); Solvent B: Acetonitrile (0.02 % TFA buffer); Solvent Gradient: Time 0: 5% B; 2.5 min: 5% B; 7 min: 95% B; Hold 95% B 5 min.

Flow Rate: 22.5 mL/min

The product peak was collected based on UV absorption and concentrated.

2. Analytical LCMS conditions:

Hewlett Packard 1100 MSD with ChemStation Software

Column: YMC ODS-AM 2.0 mm x 50 mm 5 μ column at 23°C

5 Solvent A: Water (0.02% TFA buffer)

Solvent B: Acetonitrile (0.02 % TFA buffer)

Gradient: Time 0: 5% B; 0.3 min: 5% B; 3.0 min: 90% B; Hold 95% B 2 min.

Flow rate 1.5 mL/min

Detection: 254 nm DAD; API-ES Scanning Mode Positive 150-700;
10 Fragmentor 70 mV.